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Dear Josh:

Thank you very much for your letter and for your revised discussion which I enjoyed very much reading. It is as lucid and stimulating as it could possibly be. The only remark I have is that Stasney et al. did not have DNA preparations but crude nuclear and "chromatin" fragments(p.3,l.6). You are certainly welcome to purchase any number of the entire reprint if you find it necessary.

About F_1 hybrid passage,the following was the experiment in question: S6Ca is a C3H tumor. Tested in A x C3H F_2 hybrids,it requires 3 factors. After passage through A x C3H F_1 it changed to a 1 factor tumor. We call this line S6Cb. We then inoculated a large number of F_2 bilaterally, with S6Ca on one side and S6Cb on the other. I shall call the tumors a and b in the following. We obtained mice in which both a and b grew, others in which only b grew and still others in which none of them grew. There were no animals with a growing alone. The total number of a tumors fitted well a 3-gene ratio and the total of b tumors a 1-gene ratio,just as could be expected when tested in different animals. The implication is that the one gene b requires is identical with one of the three that a required. There is no evidence for the appearance of new h-factors, I must have made some unclear statement about that. Presently, we are doing 1).reconstruction experiments,mixing b in small proportions to a (taking b from an F_2 mouse where a did not grow,and where potential a cells have thus been eliminated from the b population) to see how many b have to be present to influence the F_2-test,and 2).we are passing S6Ca through F_1 hybrids with very small inocula. If experiment 2) would show that the change still occurs,while experiment 1) would indicate that a small proportion of b cells modifies the F_2 test,selection would be definitely ruled out. As far as present evidence goes,it would seem surprising on a selection basis that the frequency of b cells is so small in the a population that it does not show up in the F_2 test and a single generation in the F_1 shifts the ratio to such an extent that a drastic change from 3 to 1 occurs. It also has to be remembered that Barrett & Deringer find that the change occurs very early during residence in the hybrids and does not increase with prolonged transfer through F_1.

Presently, I am struggling with a review article where I also discuss the phenomenon of decreased and increased specificity after passage through F_1 hybrids and some other genotypes. Here is a passage from the preliminary manuscript. All comments and criticism are heartily welcome.

"Considering the case of <u>decreased</u> specificity after F_1 passage, selective mechanisms may be operative,as suggested by Hauschka,based on preferential survival of less antigenic types in the hybrid environment. Alterna-

tively,the change may have been induced by some particularities of this tumor-host system in a certain proportion of the tumor cells. Some interesting parallels are provided by the experiments of other authors. Koprowski Under ordinary conditions the 6C3HED lymphoma cannot grow progressively in Swiss mice. Koprowski found that the tumor may acquire the capacity to do so if passed through embryonic Swiss mice for one transfer generation. Stewart has described the adaptation of Ak leukemia to unrelated strains after passage through newborn animals of the foreign genotype. Krebs et al. reported the adaptation of a mouse lymphosarcoma to foreign hosts after passage through mice that received total body X-irradiation to prevent regression. In all these cases, a tumor was exposed to a foreign genotype,but in an animal where immunological mechanisms are not fully functioning and cannot bring about tumor regression. After such passage, it acquired the capacity to grow even in immunologically active adults. In the case of Barrett and Deringer, the F_1 hybrid host cannot develop any efficient defense reaction against the C3H tumor,apparently because the histocompatibility factors of the latter are identical with those contained in the cells of the host itself in a single dose. On the other hand, the host contains some H-factors foreign to the tumor,and,as Medawar pointed out,the tumor is at least genetically qualified to react against its host. After having been exposed to the foreign H-factors in the heterozygote, the tumor becomes able to grow in the presence of some of them even when homozygous,as indicated by the increased percentage of takes in F_2 and backcross hosts. Is it possible that we are dealing with the reverse of the "acquired tolerance" phenomenon and tumors may become tolerant towards the products of foreign H-factors if exposed to them under conditions where the immunological system of the host cannot bring about tumor regression, either because it is non-functional in general as in the embryo or the irradiated mouse, or because it shares the iso-antigens of the tumor as in the F_1 hybrid?

Considering the case of <u>increased</u> specificity, it is difficult to see how any selection pressure in the hybrid host could favor cells with increased histocompatibility requirements to such a degree that the original cells of lower specificity are brought to disappearance from the population in one transfer generation. A selection theory would have to postulate their disappearance,however, since remaining cells of the original type would be selectively concentrated again when the tumor is tested in F_2 or backcross hybrids, and the change towards increased specificity could never be detected at the population level. It would appear more probable that the cells suffer some chronic damage, non-genetic in nature,during transfer in some hybrid genotypes, making them more sensitive to immunological reactions and resulting in a decreased percentage of takes when tested in segregating hybrids. Hoecker et al. have actually demonstrated the transitory nature of similar modifications,produced in leukemic cells by passage through unrelated hosts. The development of decreased specificity ("tolerance") or increased specificity ("intolerance") in a tumor after residence in foreign genotypes depends perhaps on the intensity of the reaction between the immunologically active products of tumor and host, in analogy with the reverse phenomenon of pretreatment of foreign hosts with lyophilized tissue where small doses produce immunity while large doses result in tolerance."

Do you think this is all very phantastic?

Many thanks for the terminology of transduction genetics which seems clear and logical. I hope we can apply them some day to mammalian cells. (All the IR-lines have been outcrossed with their original strain in great haste,to make the heterozygous tumors you suggested. In another year or so we may have the result of the first preliminary experiment).

With warm regards to both Esther and you,

sincerely yours,

Leo

P.S. ♀.